REMARKS/ARGUMENTS

Prior to the present amendment, Claims 41-45 and 47-52 were pending and under examination. Herewith, Claims 41-43, 45 and 47-48 have been amended. The amendment is fully supported by the claims and specification as originally filed and does not introduce any new matter. Applicants reserve the right to pursue any canceled subject matter in a continuation, continuation-in-part, and divisional application.

Applicants thank the Examiner for acceptance of the drawings filed June 30, 2009.

Objections to the Specification

The Examiner asserts that the substitute specification filed with Applicants' Response of June 30, 2009 has not been entered because it was allegedly not accompanied by a statement required under 37 CFR 1.125(b) indicating that no new matter was added.

Applicants submit that a statement under 37 CFR 1.125(b) was in fact mailed with the Response filed June 30, 2009. As evidence to that fact, Applicants provide herewith a copy of the date stamped return postcard indicating receipt of the statement along with the Response. Nevertheless, as a result of the additional objections to the specification raised by the Examiner in the present Office Action, Applicants re-submit the previously filed amendments in the presently filed substitute specification along with the statement required under 37 CFR 1.125(b).

As required, Applicants have amended the font size of all text in the specification to 12pt New Times Roman. All references to page and line numbers below are based on the marked-up copy of the substitute specification incorporating the 12pt font.

In the Office Action mailed April 1, 2009, the Examiner raised an objection to the specification as originally filed for missing text. Applicants reiterate that the missing text appears to have resulted from photocopy or scanning error. In the substitute specification provided with this response, Applicants have corrected the defect by clearly identifying the unreadable text. Applicants reiterate that the subject matter of the missing text was not actually "missing", but rather illegible, and the present amendment does not add any new matter.

In response to the Examiner's objection that the specification as originally filed is missing text, Applicants have corrected the defect by amending the following pages:

At Page 8, lines 24-29, Applicants have amended the specification to read:

... comprising a nucleic acid construct that expresses retroviral structural proteins and also comprises a retroviral vector consisting ually essentially of a promoter, nucleic acid encoding (a) a PRO polypeptide, (b) an agonist polypeptide of a PRO polypeptide or (c) an antagonist polypeptide of a PRO polypeptide, and a signal sequence for cellular secretion of the polypeptide, wherein said producer cell packages the retroviral vector in association with the structural proteins to produce recombinant retroviral particles. ...

At Page 206, lines 5 and 9, Applicants have amended the specification to read:

... 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93% nucleic acid sequence identity, alternatively at least about 94% nucleic acid sequence identity, alternatively at least about 95% nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about ...

At Page 214, line 29, Applicants have amended the specification to read:

...immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided...

At Page 215, line 1, Applicants have amended the specification to read:

...which enables the sFv to form the desired structure for antigen binding. For a review of sFv,...

At Page 255, Applicants have amended Table 6 in the specification to read:

Table 6

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	val; leu; ile	val
Arg (R)	lys; gln; asn	lys
Asn (N)	gln; his; lys; arg	gln
Asp (D)	glu	glu
Cys (C)	ser	ser
Gln (Q)	asn	asn
Glu (E)	asp	asp
Gly (G)	pro; ala	ala
His (H)	asn; gln; lys; arg	arg
Ile (I)	leu; val; met; ala; phe; norleucine	leu
Leu (L)	norleucine; ile; val; met; ala; phe	ile
Lys (K)	arg; gln; asn	arg
Met (M)	leu; phe; ile	leu
Phe (F)	leu; val; ile; ala; tyr	leu
Pro (P)	ala	ala
Ser (S)	thr	thr
Thr (T)	ser	ser
Trp (W)	tyr; phe	tyr
Tyr (Y)	trp; phe; thr; ser	phe
Val (V)	ile; leu; met; phe; ala; norleucine	leu

At Page 263, lines 23-31, Applicants have amended the specification to read:

... be a part of the PRO-encoding DNA that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, e.g., the yeast invertase leader, alpha factor leader (including *Saccharomyces* and *Kluyveromyces* α-factor leaders, the latter described in U.S. Patent No. 5,010,182), or acid phosphatase leader, the *C. albicans* glucoamylase leader (EP 362,179 published 4 April 1990), or the signal described in WO 90/13646 published 15 November 1990. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of...

At Page 272, lines 9-17, Applicants have amended the specification to read:

... (MS) and experimental autoimmune encephalomyelitis (EAE, a model for MS). A suitable procedure is described in detail in *Current Protocols in Immunology*, above, unit 4.5.

EAE is a T cell mediated autoimmune disease characterized by T cell and mononuclear cell inflammation and subsequent demyelination of axons in the central nervous system. EAE is generally considered to be a relevant animal model for MS in humans. Bolton, C., *Multiple Sclerosis* (1995) 1:143. Both [[a]] acute and relapsing-remitting models have been developed. The compounds of the invention can be tested for T cell stimulatory or inhibitory activity against immune mediated demyelinating disease using the protocol described in *Current* ...

At Page 280, lines 29-33, Applicants have amended the specification to read:

... COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences [U.S. Patent No. 4,816,567; Morrison et al., supra] or by ...

At Page 281, lines 3-4, Applicants have amended the specification to read:

... polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody ...

At Page 289, lines 17-26, Applicants have amended the specification to read:

... and γ-ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37°C, resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization

depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond ...

At Page 298, lines 5-9 and 13-14, Applicants have amended the specification to read:
... composition is used for diagnosing or treating the condition of choice. The article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, syringes, and package inserts ...

... related diseases, are excellent targets for drug candidates or disease treatment. The same proteins along with secreted proteins encoded by the genes amplified in immune related ...

At Page 306, lines 30-33, Applicants have amended the specification to read:
... concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M ...

At Page 307, lines 2-3, Applicants have amended the specification to read:
...containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C. ...

Applicants further submit that the present substitute specification includes the previously filed amendments to the Brief Description of the Drawings, incorporating where necessary a description of each figure subpart found in the replacement drawings filed June 30, 2009. Essentially, Applicants have amended the Brief Description of the Drawings in the substitute specification to correct references to figures with more than one panel, thus bringing the specification in concordance with the drawings.

In response to the Examiner's further objections identified in the Final Office Action mailed March 9, 2010, Applicants have made the following amendments:

1) The font size of all text in the specification has been amended to 12pt New Times Roman.

2) In addition, Applicants have removed the computer program listing of Table 1 from the specification in compliance with 37 CFR 1.96(c), submitted herewith the disclosure of Table 1 as a computer program listing appendix on compact disc and inserted an appropriate reference paragraph to the computer program listing appendix on compact disc at the beginning of the specification in accordance with 37 CFR 1.77(b)(5). Two identical compact discs conforming to the standards set forth in 37 CFR 1.52(e) are provided and each compact disc contains a single file entitled, "Table 1. ALIGN-2 program source code.doc". The material on the compact discs and the computer program listing appendix is intended to be incorporated-by-reference. Applicants have also amended the specification to replace previous references to Table 1 within the specification with references to the computer program listing appendix. No new matter is added by way of the Substitute Specification.

At page 1, lines 10-18, Applicants have added the following paragraph to the instant specification:

Computer Program Listing Appendix

This application contains an appendix consisting of a computer program listing over 300 lines (Appendix A). In accordance with 37 CFR 1.96(c), a computer program listing having over 300 lines must be submitted on a compact disc conforming to the standards set forth in 37 CFR 1.52(e). Two identical compact discs have been filed with the Patent & Trademark Office in accordance with Title 37 of the Code of Federal Regulations and each compact disc contains a single file entitled, "Table 1. ALIGN-2 program source code.doc". The material on the compact discs and the computer program listing appendix is hereby incorporated-by-reference.

At page 203, lines 14-17, Applicants have amended the specification to read:

... program is provided in Table 1 ~~below~~ the computer program listing appendix submitted on compact disc under the file name "Table 1. ALIGN-2 program source code.doc". The computer program listing appendix is hereby incorporated-by-reference. ...

At page 203, lines 18-19, Applicants have amended the specification to read:

... shown in Table 1 ~~below~~ of the computer program listing appendix has been filed with ...

At page 203, lines 22-23, Applicants have amended the specification to read:

... the source code provided in Table 1 ~~below~~ of the computer program listing appendix. The ALIGN-2 ...

At page 207, line 3, Applicants have amended the specification to read:

... provided in Table 1 ~~below~~ of the computer program listing appendix. The ...

At page 207, line 5, Applicants have amended the specification to read:

... shown in Table 1 ~~below~~ of the computer program listing appendix has been filed ...

At page 207, lines 9-10, Applicants have amended the specification to read:

... in Table 1 ~~below~~ of the computer program listing appendix. The ALIGN-2 program ...

Pages 220-250, disclosing Table 1, have been deleted from the specification.

Applicants request that the Examiner enter the Substitute Specification submitted herewith in compliance with 37 C.F.R. §1.125 (including both a Marked-Up Copy and a Clean Copy and a statement that the accompanying substitute specification includes no new matter).

Claim Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 45 are rejected under 35 U.S.C. §112, Second Paragraph, as being indefinite for allegedly failing to point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner asserts that "Claims [sic] 45 is confusing in reciting '5.times.' in two places and '50.mu.g/ml.'"

Applicants have amended Claim 45 to recite "5x" and "50μg/ml", respectively. Having clarified the apparent word processing errors, Applicants respectfully request reconsideration and reversal of the indefiniteness rejection of Claim 45 under 35 U.S.C. §112, second paragraph.

Claim Rejection Under 35 U.S.C. §§101 and 112, First Paragraph

Claims 41-45 and 47-52 are rejected under 35 U.S.C. §§101 and 112 because the claimed invention is allegedly not supported by either a credible, specific and substantial asserted utility or a well established utility.

Specifically, the Examiner alleges that "there is no disclosure of PRO85142 functional activity or pattern of expression in various tissues. There is no disclosure of proteins related to PRO85142 by either functional or sequence identity. The activity of PRO85142 polypeptide and its physical function are unknown." (Pages 3-4 of the instant Final Office Action). The Examiner further alleges that "[e]xpression levels of a gene encoding SEQ ID NO: 2386 is not correlated to any immune related disease in a mammal or inflammatory immune response in a mammal (claims 41and 43)." (Page 4 of the instant Final Office Action). The Examiner then concludes that "it would require further experimentation and independent inventive judgment to determine if the polypeptide of SEQ ID NO: 2386, genes encoding it, or antibodies to it could be used in the claimed methods." (Page 4 of the instant Final Office Action)

Applicants respectfully disagree and traverse the rejection on the grounds that 1) the specification provides a specific and substantial utility for the claimed methods, 2) one of ordinary skill in the art would recognize that it is "more likely than not" that cell surface markers associated with memory T cell activation are diagnostic for inflammatory immune responses and immune-related diseases and 3) the Examiner has not established a prima facie case to support his conclusion of lack of utility. Nevertheless, without acquiescing to the Examiner's assertion and merely to expedite prosecution, Applicants have amended the claims to narrow the scope of claims 41-43, which are now drawn to methods of diagnosing a memory T cell mediated immune response and diagnosing a memory T cell mediated disease, respectively. Support for these amendments can be found throughout the instant specification (see for example, page 2, lines 5-23, page 144, lines 16-39, pages191-195, and Example 1)

1. The specification provides a specific and substantial utility for the claimed methods

Applicants submit that, contrary to the Examiner's assertions, the specification clearly indicates the specific conditions that can be diagnosed with the claimed methods, that is T cell mediated immune responses and T cell mediated diseases. The asserted utility, diagnosis of T cell mediated immune responses or T cell mediated diseases, is specific to the subject matter claimed and provides a well-defined and particular benefit to the public.

In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[1,2] M.P.E.P. §2107.01 further cautions that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement.[3] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[4] gives the following instruction to patent examiners: "If the Applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility." Thus, to overcome the presumption of truth that an assertion of utility by the Applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility.

In the present application, Applicants disclose that PRO85142 is differentially expressed in isolated CD45RO T cells activated by anti-CD3/anti-CD28 as compared to: isolated resting CD45RO T cells, isolated resting CD45RA T cells and isolated CD45RA T cells activated by

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[1] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[2] *See also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (C.C.P.A. 1977).

[3] M.P.E.P. §2107.01.

[4] M.P.E.P. §2107 II(B)(1).

anti-CD3/anti-CD28. (Example 1 of the instant specification). Thus, contrary to the Examiner's assertion, there is sufficient disclosure of the expression pattern of PRO85142 in T cells. This pattern of expression is specific and reasonably corresponds to a T cell mediated immune response. Moreover, it is well established in the art that abnormal regulation or excessive stimulation of inflammatory immune responses in general, and T cell mediated immune responses in particular, often contribute to immune-related diseases.

In response to Applicants' previous arguments, the Examiner asserts that "[t]he specification does not disclose that PRO85142 is significantly overexpressed in activated CD4+ T cells as compared to resting cells." The Examiner further notes that PRO85142 is "not one of the polypeptides mentioned in the last paragraph of Example 1 in the specification." (Page 5 of the instant Final Office Action)

Applicants submit that the last paragraph of Example 1 discloses that "Below are the results of these experiments, demonstrating that various PRO polypeptides of the present invention are significantly differentially expressed ... The Figures 1-2442 show the nucleic acids of the invention and their encoded PRO polypeptides." Thus indicating that all of the sequences disclosed in the present application, including PRO85142, are differentially expressed in activated T cells. The Examiner fails to recognize the distinction that the smaller group of polypeptides further identified in Example 1 are limited to those PRO molecules that were significantly overexpressed in the assay. Applicants do not claim that PRO85142 is significantly overexpressed in activated memory T cells, but instead rely on the differential expression of PRO85142 in memory T cells for utility. One skilled in the art would understand that differential expression, manifested by either a higher or lower level of gene expression, can be diagnostic of T cell mediated immune responses. Therefore, the specification provides a specific and substantial utility for the claimed methods.

a. PRO85142 expression is diagnostic of a T cell mediated immune response

One skilled in the art understands that T lymphocytes (T cells) are an important component of a mammalian immune response. As disclosed in the specification, memory T cells, in particular, are known to be key regulators of inflammation. *In vivo,* T cells require activation through co-stimulation of cell surface receptor molecules, which results in extensive differential gene expression, cell proliferation and secretion of a variety of cytokines. These

effector molecules play a central role in the downstream activation of B cells, cytotoxic T cells and a variety of other cells which participate in the immune response. The list of costimulatory molecules is quite extensive and it is still unclear just which co-stimulatory molecules play critical roles in different types and stages of inflammation. In this application the focus is on genes which are differentially regulated by stimulation with anti-CD3 and anti-CD28 antibodies in combination and may be useful in targeting inflammatory processes which are associated with these different molecules. It should also be noted that activation of T cells typically changes the expression of several cell-surface molecules. (Immunobiology, 5th Edition, Janeway et al., Chapter 8: T Cell-Mediated Immunity). And these changes may in turn provide additional mechanisms for regulating the inflammatory immune response.

While T cells are essential components of normal immune function, it is believed that inappropriate T cell function underlies many very serious medical conditions including autoimmune disease. Diseases that are impacted by pathologic T cell function are thought to include asthma, arthritis, psoriasis, multiple sclerosis, inflammatory bowel disease, diabetes, graft versus host disease and many others. It is also well known in the art that in these diseases the portion of the T cell repertoire that has a "memory" phenotype is thought to contribute to the disease pathology. For example, Ponsford et al. (Clin Exp Immunol 2001; 124:315-322) analyzed MBP specific T-cell responses in peripheral blood samples taken directly from MS patients and healthy controls and found "MBP-reactive cells could be isolated more readily from cells enriched for the CD45RO rather than the CD45RA marker," establishing that "T cell memory for MBP exists in MS patients as reflected by an increase in activity among CD45RO cells." (see abstract and page 321, last paragraph) Robinson et al (Thorax 1993;48:26-32) teach that "selective activation of memory CD4 T cells contributes to eosinophil accumulation, bronchial hyperresponsiveness, and symptoms in asthma." (abstract) Morever, the authors assert "[t]he degree of T cell activation in broncho-alveolar lavage fluid was closely related to severity of asthma." (page 30, first paragraph of Discussion) To understand the auto-activation of T cells under the condition of SLE, Sen et al. (Immunology 2004 112 274–289) focused on the expression of several chemokine receptors and the interaction between these receptors and their ligands on CD4+ and CD8+ T cells during active and inactive disease. Their findings indicate that the frequency of CCR7+ CD8+ CD45RO+ T cells is correlated with the activity of the SLE and that the numbers of these memory T cells are significantly decreased during disease

remission. Thus, one skilled in the art would be well aware of the utility of identifying additional markers to aid in the recognition and further characterization of these important immune response mediators.

Herein, memory T cells were costimulated, leading to cell activation, and the profile of genes differentially expressed upon activation was analyzed. PRO85142 was one of the genes identified as being differentially expressed under these memory T cell activating conditions. PRO85142 (SEQ ID NO:2386) has subsequently been identified as the triggering receptor expressed on myeloid cells-like 2 protein (Official Symbol TREML2; also known as TLT2) (see NCBI BLAST analysis submitted herewith). As pointed out in the previous Response to Office Action mailed June 30, 2009, multiple studies published after the priority date of the present application confirmed that TLT2 plays important roles in immune responses associated with disease. For example, Molloy et al. reported that the Triggering Receptors Expressed on Myeloid cells (TREM), the protein family which TLT2 belongs to, are a family of activating receptors with some homology with activating natural killer cell receptors. TREM-1 is an activating receptor on neutrophils and monocytes that plays an important role in the amplification of inflammation. TREM-1 blockade significantly decreases mortality from bacterial sepsis. Altered TREM-1 expression on neutrophils in response to bacterial stimuli may be an important factor in susceptibility to bacterial infection. These receptors may potentially be manipulated to alter the inflammatory response to severe sepsis and chronic inflammation.

The Examiner asserts "[t]here is nothing in Molloy et al. and no evidence of record that SEQ ID NO: 2386 corresponds to TLT2 as argued by applicant. Molloy et al. does not appear to discuss TLT2." (Page 5 of the instant Final Office Action)

Applicants submit that a simple NCBI BLAST search of the SEQ ID NO: 2386 sequence reveals that PRO85142 corresponds to TLT2 (enclosed herewith for reference). Applicants further submit that Molloy et al. was made of record to illustrate that the TREM protein family, which TLT2 belongs to, are a family of activating receptors that play important roles in immune responses associated with disease (e.g. susceptibility to bacterial infection). Based on the teachings of Molloy about the role of the TREM protein family in inflammatory responses combined with the disclosure in the specification that PRO85142 / TLT2 is differentially expressed in memory T cells, one skilled in the art would have reason to believe that differential expression of PRO85142 / TLT2 is diagnostic of memory T cell mediated immune responses

Applicants further submit additional references herewith establishing the role of the TREM family of proteins and TLT2, in particular, in immune responses associated with disease. For example, Ford et al. (Current Opinion in Immunology 2009, 21:38–46) teach that TREM and TREM-like receptors are "pluripotent modifiers of disease through the integration of inflammatory signals with those associated with leukocyte adhesion." (abstract) More specifically, the authors establish that it is well known in the art that TLT-2 contributes to leukocyte activation, resulting in enhanced CD3-mediated IL-2 and IFN-γ production, and that *in vivo* anti-TLT-2 reduces dinitroflourobenzeneinduced contact hypersensitivity and hapten-specific IFN-g production. (see page 41, paragraph bridging columns) Hashiguchi et al. (PNAS 2008, 105(30):10495–10500) show that "TLT-2 is a counterreceptor for B7-H3, and that the interaction of B7-H3 with TLT-2 on T cells enhances T cell activation. Among the B7 family of T cell costimulatory pathways, the B7-H3:TLT-2 pathway appears to have a unique role in CD8+ T cell activation. Although TLT-2 has immune functions other than as a T cell costimulatory molecule, intervention with B7-H3:TLT-2 may represent a target for the regulation of immune responses." (see page 10499l, last paragraph column 1)

Taken together, the evidence is two-fold in support of PRO85142 as a diagnostic marker of memory T cell mediated immune responses. First, given that PRO85142 is diagnostic of the activation status of memory T cells, as disclosed in Example 1, the skilled artisan's understanding that memory T cells are key regulators of inflammation would lead them to reasonably believe that PRO85142 was diagnostic of a T cell mediated immune response. Second, subsequent research by those skilled in the art has confirmed that the TREM family of proteins, which includes PRO85142, play important roles in a variety of immune responses. In addition to the references made of record, there is a growing body of literature characterizing TLT2 in inflammatory immune responses in general and T cell mediated responses in particular. Therefore, one skilled in the art has every reason to believe that differential expression of PRO85142 is diagnostic of memory T cell mediated immune responses.

b. PRO85142 expression is diagnostic T cell mediated disease

As alluded to above, memory T cells are an important component of a mammalian immune response. It is well understood by those skilled in the art that disease or pathology occurs when these normal physiological pathways cause additional insult or injury. The

pathological condition may be directly related to the intensity of the response, a consequence of abnormal regulation or excessive stimulation, a reaction to self, or as a combination of these. Having established that PRO85142 is differentially expressed in activated memory T cells, one skilled in the art would recognize this molecule as a valuable diagnostic tool for assessing the activation status of these important immune regulators and determining whether the intensity of a given immune response is within normal bounds. Taken together with the research of record related to the TREM family of proteins, the PRO polypeptides of the present invention are useful not only as diagnostic markers for the presence of memory T cell mediated immune disorders, but also serve as therapeutic targets for the treatment of those diseases. Essentially, where one finds a disregulated immune-inflammatory response associated with a disease condition, modulation of that response would be of therapeutic benefit.

A variety of T-cell mediated immune-related diseases and disorders are disclosed in the specification of the instant application. T cell mediated diseases, including those characterized by infiltration of inflammatory cells into a tissue, involve stimulation of T cell proliferation, inhibition of T-cell proliferation, increased or decreased vascular permeability or the inhibition thereof. Specifically, the instant specification indicates that diseases that are impacted by pathologic T cell function are thought to include asthma, arthritis, psoriasis, multiple sclerosis, inflammatory bowel disease, diabetes and graft versus host disease and that among these diseases memory T cells are thought to contribute to the disease pathology.

Knowing that PR85142 is differentially expressed in the activated memory T cell, a skilled artisan would recognize that PRO85142 is diagnostic of memory T cell mediated immune responses and thus can be used as a diagnostic marker for memory T cell mediated diseases. Contrary to the Examiner's assertion that the diagnostic use must be limited to a single type of immune-related disease in order to meet the requirement of "specific utility," neither law nor the utility guideline prohibit a patentable invention from having multiple utilities.

2. *It is "more likely than not" that cell surface markers associated with T cell activation are diagnostic for T cell mediated immune responses and T cell mediated diseases*

In *Cross v. Iizuka,*[5] the C.A.F.C. reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, *i.e.,* there is a reasonable correlation there between."[6] The Court perceived, "No insurmountable difficulty" in finding that, under appropriate circumstances, "*in vitro* testing, may establish a practical utility."[7] Moreover, the Applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." In re Irons,340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. Nelson v. Bowler, 626 F.2d 853, 856-57, 206 USPQ 881, 883-84 (CCPA 1980)

Applicants reiterate that studies published after the priority date of the present application suggest that the TREM family of proteins, which includes PRO85142 / TLT2, play important roles in immune-related diseases. These reports confirm the disclosure in the specification that PRO85142 is involved in T cell mediated immune responses and thus diagnostic of T cell mediated diseases. The Examiner is further reminded that the T cell activation protocol applied in the present application is representative of a commonly used *in vitro* model based on well studied cellular activation mechanisms. As determined by the courts, *in vitro* testing may establish a practical utility[8]. Example 1 demonstrates that PRO85142 is diagnostic of the activation status of memory T cells and the skilled artisan's understanding that memory T cells are key regulators of inflammation would lead them to believe that PRO85142 was diagnostic of a memory T cell mediated immune response and useful for determining whether the intensity of

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[5] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[6] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[7] *Id.*

[8] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

a given immune response is within normal bounds or diagnostic of disease. Therefore, the claimed invention has specific and substantial utility.

3. A prima facie case of lack of utility has not been established

The PTO has the initial burden to prove that Applicants' claims of usefulness are not believable on their face.[9] Thus, to overcome the presumption of truth that an assertion of utility by the Applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Applicant. The issue will then be decided on the totality of evidence.

To properly reject a claimed invention under 35 U.S.C. 101, the Office must (A) make a prima facie showing that the claimed invention lacks utility, and (B) provide a sufficient evidentiary basis for factual assumptions relied upon in establishing the prima facie showing. *In re Gaubert*, 524 F.2d 1222, 1224, 187 USPQ 664, 666 (CCPA 1975) ("Accordingly, the PTO must do more than merely question operability - it must set forth factual reasons which would lead one skilled in the art to question the objective truth of the statement of operability"). If the Office cannot develop a proper prima facie case and provide evidentiary support for a rejection under 35 U.S.C. 101, a rejection on this ground should not be imposed. See, e.g., In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992)

Applicants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Having established that PRO85142 is differentially expressed in activated memory T cells, one skilled in the art would recognize this molecule as a valuable diagnostic tool for assessing the activation status of these important immune regulators. This biological activity is specific and reasonably corresponds to a memory T cell mediated immune response. Moreover, it is well established in the art that abnormal regulation or excessive stimulation of inflammatory immune responses often contribute to immune-related diseases. Therefore, Applicants submit that determining the

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[9] *Ibid.*

expression level of the gene encoding the PRO85142 polypeptide has utility in the diagnosis of memory T cell mediated diseases. Based on such a utility, one of skill in the art would know exactly how to use the claimed method for diagnosis of memory T cell mediated immune responses and memory T cell mediated diseases, without any undue experimentation.

Accordingly, Applicants respectfully request reconsideration and reversal of the utility/enablement rejection of Claims 41-45 and 47-52 under 35 U.S.C. §§101 and 112, first paragraph.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **50-2389** (referencing Attorney's Docket No. **24126-156/GNE-0269 R1**).

Respectfully submitted,

Date: August 9, 2010

By: _____
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